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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,489	03/01/2004	Serge Carillo	ST94037B/80375.0033	9027

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/788,489	**Applicant(s)** CARILLO ET AL.	
	Examiner SCOTT LONG	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 October 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/SCOTT LONG/
Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because:

The applicant has not presented any claim amendments. However, the applicant has requested reconsideration of the pending rejection based on arguments presented 10/21/2009.

Claims 1-8 remain rejected under 35 U.S.C. 103(a) as being obvious over Ramsby et al. (Electrophoresis. Feb 1994; 15(2): 265-277) and further in view of Robaye et al. (Electrophoresis. 1994; 15: 503-510) and further in view of Squier et al. (Journal of Cellular Physiology, May 1994; 159(2): 229-237) and further in view of Lowe et al. (Nature. 29 April 1993; 362: 847-849). further in view of Lane et al (British Medical Bulletin. 1994; 50(3):582-599). for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant states "the cited art, as detailed below, refers only to preventing apoptotic conditions." (Remarks, page 2, line 16). The examiner notes that the instant claims are directed to a method for detecting an inhibitor of p53 in a cell extract by administering a protein inhibitor of calpain protease activity to the cell extract and measuring p53 and its fragments. Contrary to the applicant's characterization, the cited art, like the instant claims, describe methods of detecting inhibitors of proteolysis. The cited art is are directed to methods of "detection and monitoring of cellular enzyme pools or enzyme-inhibitor dynamics" (Ramsby, page 276, col.2, lines 12-13), "proteolysis can be detected by 2DE" (Robay, page 503, col.1, line 33), western blots show "unautolyzed or pro-form calpain 1 can be detected in thymocyte cytosols" (Squier, page 232, col.1, line 18) and "cell extracts were prepared and assayed for proteolysis" (Squier, page 230, col.1, calpain activity assays.) Therefore, the examiner finds the applican't's premise that the cited art is NOT directed to methods of detection to be inaccurate. The cited art is directed to methods of detecting inhibitors of protein degradation and particularly to calpain inhibitors such as calpastatin. Furthermore, the cited art indicates that calpain protease activity degrades p53. Therefore, the examiner finds the applicant's characterization of the cited art unpersuasive.

The applicant further argues that the cited art does not teach or suggest "administering a peptide or protein inhibitor of calpain protease activity to the cell extract" (Remarks, page 2 bridging page 3). The applicant states, "Applicants specifically request the column/line citation of the reference that the Examiner alleges teaches 'administering a peptide or protein inhibitor of calpain protease to the cell extract'" (Remarks, page 3, parag.2). Rambsy et al. teach calpastatin is an inhibitor of calpain (page 271, col.1, 2nd parag.). Therefore, a skilled artisan knows that calpastatin is a protein inhibitor of calpain protease activity. Squire et al. teach that apoptosis is blocked by specific inhibitors of calpain (abstract). Squire et al. provide a method for assaying proteolysis in cells treated with Calpain Inhibitor I, a protein inhibitor of calpain, prior to performing a Western Blot on the cell extracts (page 230, Calpain activity assays). In the case of Squire et al., the protein inhibitor of calpain protease activity is in the cell extract but was administered to the cells prior to extraction. Rambsy teaches that EDTA was added to the cell extract to inhibit calpain and further indicates that calpastatin is released by the cells into the cell extract during extraction with digitonin/EDTA (page 271, col.1, parag.1). Therefore, Rambsy indirectly practices the second step of claim 1 (administering a calpain inhibitor) during the process of performing the 1st step (providing a cell extract). Furthermore, it is clear to a skilled artisan that Rambsy recognizes the value and importance of calpastatin for inhibiting proteases in the cell extract. Therefore, this cannot be the point of novelty in the claimed invention. For these reasons and the others provided in the pending rejection, the examiner concludes a skilled artisan would read the cited art and practice the claimed invention. Therefore, the examiner finds the applicant's arguments unpersuasive.

The applicant further argues (pages 3-5) that the cited art teaches away from the instant invention. For example, the applicant states "one of the objects of the Applicants' invention is to trigger apoptosis in tumor cells by using calpain inhibitors to prevent calpain degradation of wild-type p53" (Remarks, page 4). The examiner points out that the instant method claims to be using a cell extract. Therefore, there can be no "triggering of apoptosis in tumor cells," since the cells no longer exist. It seems the applicant is discussing some type of method of treatment, instead of the method for detecting inhibitors of p53 degradation, as claimed. Therefore, the examiner concludes that the applicant is engaging in spurious argument. Accordingly, the examiner finds the applicant's arguments unpersuasive.

The applicants further object to the use of Rambsy in the obviousness rejection and "respectfully request that the examiner explain why a person having ordinary skill in the art in the field would consult a source discussing differential detergent fractionation of hepatocytes." (Remarks, page 5 bridging page 6). Rambsy teaches that Two-dimensional gel electrophoresis is often used to assess protein degradation (abstract). Rambsy teaches that inhibition of calpain affects protein degradation and further teaches that p53 is one of the proteins detected using their methods. Rambsy teaches that EDTA was added to the cell extract to inhibit calpain and further indicates that calpastatin is released by the cells into the cell extract during extraction with digitonin/EDTA (page 271, col.1, parag.1). It was known in the art that calpain and p53 were involved in apopotosis. Rambsy teaches that calpastatin is an inhibitor of calpain proteolysis. Therefore, a skilled artisan seeking to develop an assay measuring degradation of p53 by calpain would, at least, read Rambsy in his quest to devise a method for detecting inhibitors of p53 degradation. Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-8 under 35 U.S.C. 103(a) as being obvious over Ramsby et al. in view of Robaye et al. and further in view of Squier et al. and further in view of Lowe et al. further in view of Lane et al.

/SDL/.